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Limb Defects and Congenital Anomalies of the Genitalia in an Infant With Homozygous α-Thalassemia

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We describe an infant with homozygous α-thalassemia, genital abnormalities, and terminal transverse limb defects, whose limbs demonstrate evidence of loss of tissue and abnormal morphogenesis. We propose these defects were due to either severe fetal anemia or to vascular occlusion by abnormal erythrocytes, resulting in hypoxia of the developing distal limbs and genitalia. Am. J. Med. Genet. 68:158–161, 1997

KEY WORDS: α-thalassemia; limb defects; hypospadias; ambiguous genitalia

INTRODUCTION

Homozygous α-thalassemia usually is lethal in the perinatal period, although there have been occasional long-term survivors [Beaudry et al., 1986; Bianchi et al., 1986; Lam et al., 1992]. These infants require lifelong transfusion therapy, but there is little information available about other problems, including congenital anomalies in these children. Our patient was diagnosed prenatally as having α-thalassemia and received intrauterine transfusions. At birth, he was found to have limb and genital defects and later showed evidence of developmental delay.

CLINICAL REPORT

This male infant was born to healthy Filipino parents. Their first pregnancy had resulted in a hydropic stillborn infant at 28 weeks of gestation. Autopsy and hemoglobin electrophoresis showed homozygous α-thalassemia. The parents received genetic counseling and carrier testing which indicated that they were both heterozygous carriers of the Southeast Asian α-thalassemia-1 deletion ($\alpha\alpha/-^{SEA}$). During the next pregnancy, amniocentesis at 16 weeks showed the fetus to be homozygous for the deletion ($-^{SEA}/-^{SEA}$) and was therefore predicted to be affected with α-thalassemia. At 25 weeks, fetal ascites was noted. Intrauterine transfusions were given at 26, 27, and 32 weeks, with resolution of the ascites and normal fetal growth [Carr et al., 1995]. The mother was given betamethasone before a planned Caesarean section delivery at 34 weeks. The baby weighed 2,100 g and had mild respiratory distress treated by continuous positive airway pressure ventilation for 5 days.

Hemoglobin electrophoresis showed 40.6% Hb A1 (from the intrauterine transfusions), 59.4% Hb Barts, and no Hb F. Facial appearance was normal, but there were abnormalities of the limbs and genitalia. There was a terminal transverse defect of the left lower limb with absence of most of the distal ⅓ of the foot except for a rudimentary fifth toe (Fig. 1). Radiographs showed a single distal phalanx and absence of the second to fourth metatarsals. On the right foot, there was partial syndactyly of the second and third toes with mild hypoplasia of the third toe. The hands had bilateral bridged horizontal palmar creases. The left hand had mild hypoplasia and partial cutaneous syndactyly of the second, third and fourth fingers (Fig. 2). Examination of the genitalia showed mild hypospadias with a dorsal hood and an incompletely descended right testicle.

Results of cranial ultrasound examination were normal. He was discharged at 11 days and has received periodic blood transfusions. He has been growing below, but parallel to, the 3rd centiles for height, weight, and head circumference. Psychological testing at 21 months showed developmental delay. The Bayley II Scales of Infant Development showed cognitive functioning at about a 16 month level. The Peabody Developmental Gross and Fine Motor Scales showed age equivalents of 7 and 16 months, respectively.

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Fig. 1. Terminal transverse defect of the left foot and syndactyly of toes two and three of the right foot.

DISCUSSION

Terminal transverse limb defects can be caused by teratogens, genetic factors, hypoxia, and by disruptive forces, such as abnormalities within the vasculature of the developing limbs or external compression from amniotic bands. The limbs are formed from the apical ectodermal ridge. The limb buds appear at about 4 weeks of embryonic life, the finger rays appear by 6 weeks, and the digits become separate by 7 to 8 weeks. Interruption of development, obstruction, or damage to the embryonic blood vessels during this time can produce various types of limb reduction defects, depending on the timing and severity of the abnormality [Van Allen, 1992]. Digital anomalies can also be produced by early chorionic villus sampling, which is thought to produce transient vasoconstriction of placental vessels [Burton et al., 1992], and in rabbits by maternal hypotension [Danielsson et al., 1989]. There are also several syndromes or sequences which involve the limbs plus other parts of the body. The Poland sequence (absent or hypoplastic pectoralis muscle with syndactyly, hypoplasia or transverse limb reduction defects) is thought to be due to disruption of the embryonic subclavian artery during the sixth week of gestation, and the Möbius sequence (cranial nerve palsies with or without limb defects) is thought to be due to premature regression or obstruction of the primitive trigeminal arteries before the establishment of sufficient blood supply from the vertebral arteries [Bavinck and Weaver, 1986].

Fig. 2. Partial cutaneous syndactyly on the left hand.

During embryonic life, globin chain synthesis begins in the yolk sac from the 3rd to 8th weeks of gestation [Miller, 1995]. The first hemoglobins synthesized contain the embryonic chains, epsilon (ϵ) and zeta (ζ), which combine with each other and with α or gamma (γ) chains to form three embryonic hemoglobins, Gower I (ζ ϵ2), Gower 2 (α2 ϵ2), and Hb Portland (ζ2 γ2). At about the 5th week of gestation, the major site of hematopoiesis switches from the yolk sac to the liver. At the same time ζ chains begin to be replaced by α chains and ϵ chains by γ chains, permitting synthesis of the major fetal hemoglobin, HbF (α2 γ2) by around 10 weeks.The embryonic red cells produced are normally macrocytic. In fetuses affected with homozygous α-thalassemia, the absence of α chains prevents synthesis of Hb Gower 2, Hb F, and normal adult hemoglobin. Thus, the erythrocytes produced at the time of limb formation could be abnormal in number and/or in structure. By term, they have mainly Hb Barts (a tetramer of γ chains) and a small amount of Hb Portland. Hb Barts has a higher oxygen affinity than normal fetal hemoglobin so that oxygen is released poorly to the fetal tissues. Affected infants develop high output cardiac failure, hydrops, and either stillbirth or neonatal death.

Infants with α-thalassemia have been found to have a higher than expected incidence of congenital abnormalities [Liang et al., 1985; Guy et al., 1985; Nakayama et al., 1986], especially of the limbs and genitalia (Table I). Autopsy description of one affected fetus showed limb defects remarkably similar to our case (absence of toes 1–4, syndactyly of toes 2 and 3 on the other foot, and "spade-like fingers"), which were thought to be due to intrauterine anoxia from severe fetal anemia [Chitayat et al, 1994]. Harmon, Osathanondh, and Holmes [1995] observed a 20-week fetus presumed to be an α-thalassemia homozygote, with symmetrical terminal transverse defects consisting of absent hands and forefeet with digit-like nubbins on each limb. Pathologic examination was consistent with infarcted blood vessels, which suggested another possible mechanism, i.e., occlusion of the digital arteries by abnormally large red cells because of megaloblastic erythrocytosis. A similar phenomenon has been produced in rabbits whose offspring demonstrated congenital limb deficiency associated with severe polycythemia and macrocytosis. These limb defects could be prevented by treating the pregnant rabbits with folic acid [Petter et al., 1977].

Another striking association with homozygous α-thalassemia, is undermasculinization or ambiguous genitalia, first observed in two of five cases reported by Guy et al. [1985]. In a larger series of 46 hydropic in-

TABLE I. Limb and Genital Defects in Homozygous α-Thalassemia

Limb abnormality	Genital abnormality	Subjects	Outcome
Transverse limb defects, hands and feet	None noted	38 week hydropic male	Pregnancy terminated
Fingers spade-like, reduction amputation 1st–4th toes, syndactyly 2nd–3rd toes[a]		33 week female	Neonatal death
None noted[b]	Hypospadias	32–34 week hydropic live-born male	Delayed development
None noted	Ambiguous genitalia, 46,XY karyotype	1,490 g stillborn	
None noted[c]	Ambiguous genitalia	27 week hydropic infant	Neonatal death
Symmetrical absence of hands and forefeet with digit-like nubbins[d]		20.7 week hydropic female infant	Pregnancy terminated
Phocomelia Digital deformity, two cases Bilateral talipes equinovarus[e]	Hypospadias	Series of 46 hydropic infants, 19 males, 26 females, one sex not recorded	22 stillborn, 24 neonatal deaths
None noted[e]	Three with ambiguous genitalia, one with hypospadias and chordee, three phenotypic females with intraabdominal testes	Series of 18 hydropic infants	10 stillborn, 8 lived for 30 minutes to 2 days
Limb defects, one hand and both feet[f]	Hypospadias, incompletely descended testicle	Liveborn after intrauterine transfusions	Delayed development

[a] Chitayat et al., 1994.
[b] Beaudry et al., 1986.
[c] Guy et al., 1985.
[d] Harmon et al., 1995; Liang et al., 1985.
[e] Nakayama et al., 1986.
[f] This report.

fants [Liang et al., 1985], one was noted to have hypospadias, but there was an increased incidence of female births (which may have been due to some chromosomal XY males being incorrectly assigned female gender because of undermasculinized genitalia). In a third study [Nakayama et al., 1986], autopsies of 16 hydropic fetuses showed anomalous genitalia in 6; 1 had hypospadias, 3 males had ambiguous external genitalia, and 2 phenotypic females had intra-abdominal testes. The only reported male long-term survivor [Beaudry et al., 1986] also had hypospadias. The mechanism for the abnormal sexual differentiation in homozygous α-thalassemia may be vascular compromise and tissue ischemia. Intrauterine localized ischemia of the corpus spongiosum and urethra in experimental animals can cause hypospadias [Kizilcan et al., 1994]. Interestingly, there is a high incidence of genital anomalies in males with the X-linked α-thalassemia mental retardation (ATR-X) syndrome [McPherson et al., 1995], including hypospadias, ambiguous genitalia, and female gender assignment. Although there is no deletion of alpha-globin genes, their expression is suppressed, perhaps by other genes which act as transcriptional regulators [Gibbons et al., 1995]. Another condition, congenital dyserythropoietic anemia type I, has been reported in association with limb reduction defects in two patients [Brichard et al., 1994]. The authors did not speculate on the pathogenesis, but the erythrocytes in both patients were macrocytic.

In our patient, early anemia may have resulted in hypoxia of the developing distal limbs. Another possibility is vascular occlusion by embryonic erythrocytes that were either larger than normal and/or less deformable than normal erythrocytes. Since the microcirculation in the distal limbs, the genitalia, and the brain is an end-artery type, without extensive collaterals, these organs are particularly susceptible to vascular compromise. Vascular occlusion or anemia that occurred during the early development of distal limb structures could have caused malformations by interrupting the normal process of development, leading to cutaneous syndactyly of the fingers. Vascular occlusion later on in time could have led to disruption of a structure that had previously developed normally, thus causing the reduction defect of the foot.

This case illustrates that the consequences or associations of this hemoglobinopathy can include malformations and disruptions in the formation of the limbs and male genitalia. It is not clear whether the developmental delay seen in our patient is related to vascular insufficiency during early cerebral development, to chronic hypoxia during the latter part of the pregnancy, or possibly to both factors. We conclude that information on the risk of congenital anomalies should be included in the genetic counseling for parents considering the option of intrauterine transfusions or hoping for eventual gene therapy for offspring with α-thalassemia.

REFERENCES

Bavinck JNB, Weaver D (1986): Subclavian artery supply disruption sequence: Hypothesis of a vascular etiology for Poland, Klippel-Feil, and Möbius anomalies. Am J Med Genet 23:903–918.

Beaudry MA, Ferguson DJ, Pearse K, Yanofsky RA, Rubin EM, Kan YW (1986): Survival of a hydropic infant with homozygous α-thalassemia. J Pediatr 108:713–716.

Bianchi DW, Beyer EC, Stark AR, Saffan D, Sachs BP, Wolfe L (1986): Normal long-term survival with α-thalassemia. J Pediatr 108: 716–718.

Brichard B, Vermylen C, Scheiff JM, Michaux JL, Ninane J, Cornu G (1994): Two cases of congenital dyserythropoietic anaemia type I associated with unusual skeletal abnormalities of the limbs. Br J Haematol 86:201–202.

Burton BK, Schulz CJ, Burd LI (1992): Limb anomalies associated with chorionic villus sampling. Obstet Gynecol 79:726–730.

Carr S, Rubin L, Dixon D, Star J, Dailey J (1995): Intrauterine therapy for homozygous α-thalassemia. Obstet Gynecol 85:876–879.

Chitayat D, Babul R, Wyatt P, Waye JS, O'Brien K, Chui DHK, Conacher S, Silver M (1994): Limb reduction defects in α-thalassemia homozygotes. Teratology 49:405.

Danielsson BRG, Reiland S, Rundqvist E, Danielson M (1989): Digital defects induced by vasodilating agents: Relationship to reduction in uteroplacental blood flow. Teratology 40:351–358.

Gibbons RJ, Picketts DJ, Villard L, Higgs DR (1995): Mutations in a putative global transcriptional regulator cause X-linked mental retardation with α-thalassemia (ATR-X syndrome). Cell 80: 837–845.

Guy G, Coady DJ, Jansen V, Snyder J, Zinberg S (1985): α-thalassemia hydrops fetalis: Clinical and ultrasonographic considerations. Am J Obstet Gynecol 153:500–504.

Harmon JV, Osathanondh R, Holmes LB (1995): Symmetrical terminal transverse limb defects: Report of a twenty-week fetus. Teratology 51:237–242.

Kizilcan F, Tanyel FC, Cakar N, Buyukpamuku N, Hicsonmez A (1994): The effect of intrauterine vascular compromise on further development of corpus spongiosum and urethra. Eur J Pediatr Surg 4:26–29.

Lam TK, Chan V, Fok TF, Li CK, Feng CS (1992): Long-term survival of a baby with homozygous alpha-thalassemia-1. Acta Haematol 88:198–200.

Liang ST, Wong VCW, So WWK, Ma HK, Chan V, Todd D (1985): Homozygous α-thalassemia: Clinical presentation, diagnosis and management. A review of 46 cases. Br J Obstet Gyn 92:680–684.

McPherson EW, Clemens MM, Gibbons RJ, Higgs DR (1995): X-linked α-thalassemia/mental retardation (ATR-X) syndrome: A new kindred with severe genital anomalies and mild hematologic expression. Am J Med Genet 55:302–306.

Miller DR (1995): Origin and development of blood cells and coagulation factors: Maternal and fetal interactions. In Miller DR, Baehner RL (eds): "Blood Diseases of Infancy and Childhood," Seventh Edition. St. Louis: Mosby-Yearbook, Inc., pp 3–29.

Nakayama R, Yamada D, Steinmiller V, Hsia E, Hale RW (1986): Hydrops fetalis secondary to Bart hemoglobinopathy. Obstet Gynecol 67:176.

Petter CJ, Bourbon JP, Maltier, Jost A (1977): Simultaneous prevention of blood abnormalities and hereditary congenital amputation in a brachydactyous rabbit stock. Teratology 15:149–157.

Van Allen MI (1992): Structural anomalies resulting from vascular disruption. Pediatr Clin North Am 39:255–277.